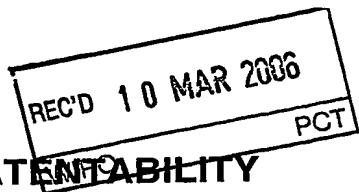


## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)



## (PCT Article 36 and Rule 70)

|   |  |  |                       |
|---|--|--|-----------------------|
| Applicant's or agent's file reference<br>CJG/PB60626  | <b>FOR FURTHER ACTION</b>                                |  | See Form PCT/IPEA/416 |
| International application No.<br>PCT/EP2004/014380  | International filing date (day/month/year)<br>15.12.2004 | Priority date (day/month/year)<br>17.12.2003 |                       |
| International Patent Classification (IPC) or national classification and IPC<br>INV. C07D223/16 C07D405/12 C07D401/04 C07D413/12 C07D403/12 C07D409/12 C07D471/04 C07D417/12<br>C07D401/14 C07D401/12 C07D403/14 C07D405/14 A61K31/55 A61P25/28 |  |  |                       |
| Applicant<br>GLAXO GROUP LIMITED  |  |  |                       |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
  - a.  (*sent to the applicant and to the International Bureau*) a total of 1 sheets, as follows:
    - sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
    - sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
  - b.  (*sent to the International Bureau only*) a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
  - Box No. I Basis of the report
  - Box No. II Priority
  - Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - Box No. IV Lack of unity of invention
  - Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - Box No. VI Certain documents cited
  - Box No. VII Certain defects in the international application
  - Box No. VIII Certain observations on the international application

|  |  |
|--|--|
| Date of submission of the demand<br><br>17.10.2005   | Date of completion of this report<br><br>09.03.2006                            |
| Name and mailing address of the International preliminary examining authority:<br><br><br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br><br>Kollmannsberger, M<br>Telephone No. +49 89 2399-7364 |

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/EP2004/014380

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on

- the international application in the language in which it was filed
- a translation of the international application into , which is the language of a translation furnished for the purposes of:
  - international search (under Rules 12.3(a) and 23.1(b))
  - publication of the international application (under Rule 12.4(a))
  - international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-59 as originally filed

**Claims, Numbers**

2-8 as originally filed  
1 received on 20.10.2005 with letter of 17.10.2005

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3.  The amendments have resulted in the cancellation of:

- the description, pages
- the claims, Nos.
- the drawings, sheets/figs
- the sequence listing (*specify*):
- any table(s) related to sequence listing (*specify*):

4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- the description, pages
- the claims, Nos.
- the drawings, sheets/figs
- the sequence listing (*specify*):
- any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/EP2004/014380

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,  
 claims Nos. 7

because:

- the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- no international search report has been established for the said claims Nos.
- a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.
- a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT  
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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

|                               |      |        |         |
|-------------------------------|------|--------|---------|
| Novelty (N)                   | Yes: | Claims | 1-9     |
|                               | No:  | Claims |         |
| Inventive step (IS)           | Yes: | Claims | 1-9     |
|                               | No:  | Claims |         |
| Industrial applicability (IA) | Yes: | Claims | 1-6,8,9 |
|                               | No:  | Claims |         |

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

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**Re Item III**

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

**Re Item V**

**V-1. State of the art**

The following documents have been cited:

- D1: WO 96/05194 A (DR. KARL THOMAE GMBH) 22 February 1996 (1996-02-22)
- D2: WO 03/068751 A (GLAXO GROUP LIMITED; BROMIDGE, STEVEN, MARK; JOHNSON, CHRISTOPHER, NOR) 21 August 2003 (2003-08-21)
- D3: WO 03/095428 A (GLAXO GROUP LIMITED; GRIBBLE, ANDREW, DERRICK; FORBES, IAN, THOMSON; L) 20 November 2003 (2003-11-20)
- D4: EP-A-1 331 010 (TAKEDA CHEMICAL INDUSTRIES, LTD) 30 July 2003 (2003-07-30)
- D5: STARK H: "Recent advances in histamine H3/H4 receptor ligands" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 13, no. 6, 2003, pages 851-865, XP002298271 ISSN: 1354-3776
- D6: WO 2004/056369 A (GLAXO GROUP LIMITED; BAMFORD, MARK, JAMES; DEAN, DAVID, KENNETH; SEHMI) 8 July 2004 (2004-07-08)

D6 has been published after the priority date and is disregarded during the PCT procedure.

**V-2. Novelty (Art. 33(2) PCT):**

D1 discloses synthesis a synthesis intermediate which has been excluded from the scope of the present claims by means of a disclaimer (see p. 57 compound (1)). The

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general formula (p. 31 structure (III)) overlaps with formula (I) of claim 1 for  $r_2=C_1-C_6$ -alkyl substituted by  $CO_2R_8$ . However, there is no example compound disclosed in the overlapping region (p.65 compound (1)) differs in that  $R_2$  cannot be a cyclohexyl substituted by 2-(methoxycarbonyl)ethyl group) and the general formula of D1 nor is there a specific disclosure of the overlap. The overlap is thus seen as a novel selection from D1.

The claims differ from D2 and D3 due to the absence of the cycloalcyl moiety for  $R_1$ . D4 overlaps generically with the presently claimed compounds and their use for treating neurological diorders (see e. g. structure (IIc) on page 58) if  $R_2$  is an amino-substituted grouop, but no example of D4 is close to the present claims and the definitions of D4 would have to be assembled from a multitude of lists in order to arrive at the claimed overlap. The overlap can be seen as a novel selection. D5 does not disclose benzazepine derivatives.

**V-3. Inventive step (Art. 33(3) PCT)**

The present application deals with histamine h3 antagonists/inverse agonists and their use in the treatment of neurological, in particular neurodegerative diseases.

D5 is seen as closest prior art since D5 also deals with histamine h3 receptor ligands. D5 is a review published shortly before the priority date of the present application and summarizes the research on histamine h3/h4 receptor ligands. D5 does not dicclose benzazepine derivatives.

The problem to be solved by the present application is thus the provision of further histamine h3 receptor ligands. Although the use of certain benzazepines for the treatment of neurological disorders is known from D2-D4, from the cited documents a man skilled in the art could not predict that benzazepines, and in particular 7-amino-3-cycloalkyl-3-benzazepines would have such an effect because neither discloses the prior art benzazepines as histamine receptor antagonists nor is there a disclosure of cycloalcyl-substituted benzazepines in the treatment of neurological disorders. The compounds of D1 are disclosed as synthesis intermediates.

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The claims fulfil thus Art. 33(3) PCT.